

REMARKS

Amendments to the specification

The specification has been amended to indicate the priority claim in the current application as well as to update the status of the applications listed.

Amendments to the claims

New claims 13-17 are presented above. The new claims have been added to ensure that claims corresponding to issued claims in U.S. Patent 6,472,185 have been presented for examination within one year of the date of issuance as required by 35 U.S.C. §135(b).

Support for the new claims may be found as shown in the following chart:

Claim	Support in Specification
13. A composition comprising at least two oligonucleotide probes, which specifically hybridize to a polymorphism in a DNA sample,	<p>Page 4, line 35-page 5, line 4: Oligonucleotide probes have long been used to detect complementary nucleic acid sequences in a nucleic acid of interest (the "target" nucleic acid). In some assay formats, the oligonucleotide probe is tethered, i.e., by covalent attachment, to a solid support, and <i>arrays of oligonucleotide probes immobilized on solid supports have been used to detect specific nucleic acid sequences in a target nucleic acid.</i></p> <p>Page 23, lines 16-24: Genetic linkage markers are defined as highly polymorphic sequences which are uniformly distributed throughout a genome. In an additional embodiment, <i>the methods of the present invention are used to identify and define these polymorphic markers.</i> Because these markers are identified and defined by their proximity to type-II restriction sites, they are referred to herein as restriction site sequence <i>polymorphisms</i></p>

	<p>("RSSPs"). In general, these RSSP markers are identified by comparing <i>captured</i> sequences among two genomes.</p>
<p>and an amplified mixture of DNA isolated from a genome, wherein the amplified mixture of DNA is made by cleaving a genomic DNA sample with at least one restriction enzyme, thereby providing restriction fragments;</p> <p> ligating adapter nucleic acids to the DNA restriction fragments;</p>	<p>Page 10, lines 5-16: More particularly, this method comprises <i>first treating the polynucleotide sequence with a first Type-IIIs endonuclease having a specific recognition site on the sequence, thereby cleaving the sequence. A first "adapter sequence" which comprises a second Type-IIIs endonuclease recognition site is ligated to the cleaved sequence.</i> The resulting heterologous sequence thus has an ambiguous sequence sandwiched between two different Type-IIIs endonuclease recognition sites. This resulting sequence is then treated with a second Type-IIIs endonuclease specific for the ligated recognition site, thereby cleaving the sequence. <i>A second adapter sequence is then ligated to this cleaved sequence.</i></p>
<p>providing primers that are complementary to the adapter nucleic acids; and,</p>	
<p> amplifying the DNA restriction fragments by the polymerase chain reaction by extending the primers, thereby providing the amplified mixture of DNA.</p>	
<p>14. The composition of claim 13, wherein the at least two oligonucleotides are immobilized on a solid support.</p>	<p>Page 4, line 35-page 5, line 4: Oligonucleotide probes have long been used to detect complementary nucleic acid sequences in a nucleic acid of interest (the "target" nucleic acid). In some assay formats, the oligonucleotide probe is tethered, i.e., by covalent attachment, to a solid support, and <i>arrays of oligonucleotide probes immobilized on solid supports have been used to detect specific nucleic acid sequences in a target nucleic acid.</i></p>
<p>15. A method of characterizing a</p>	<p>Page 21, lines 20-28:</p>

nucleic acid, comprising:
providing at least one oligonucleotide probe which specifically hybridizes to a polymorphic genetic linkage marker in a genomic DNA sample;

The combination of these mapping techniques with oligonucleotide arrays provides the capability of *identifying a large number of genetic markers* on a particular sequence. Typically, a genomic fragment will have more than one, and even several Type-IIs restriction sites within its sequence. Thus, when *probed with an oligonucleotide array, the captured sequences from a particular genomic fragment will hybridize with a number of probes on the array, producing a distinctive hybridization pattern.*

Page 23, lines 16-20:
Genetic linkage markers are defined as highly polymorphic sequences which are uniformly distributed throughout a genome. In an additional embodiment, the methods of the present invention are used to identify and define these polymorphic markers.

amplifying a mixture of nucleic acids comprising a group of genome fragments comprising polymorphisms, thereby providing an amplified nucleic acid mixture of genome fragments; and

Page 25, lines 10-16:
a subset of genomic DNA which is identified by the presence of a type-IIs recognition site is *amplified* (FIG. 8A), *DNA containing polymorphisms within the amplified subset are isolated* (FIG. 8B), and the sequences adjacent to the type-IIs recognition site in the isolated polymorphism-containing sequences are identified and characterized (FIG. 8C).

hybridizing the at least one oligonucleotide probe to the amplified nucleic acid mixture, thereby detecting at least one nucleic acid fragment in said amplified mixture.

Page 25, lines 10-16:
See passage above

16. The method of claim 15, wherein the oligonucleotide probe is a member of an array of oligonucleotide probes, which array comprises additional oligonucleotide probes which hybridize to one or more polymorphic

Page 25, lines 10-16:
See passage above

genetic linkage markers.

17. The method of claim 15, wherein the amplified nucleic acid mixture is made by cleaving a genomic DNA sample with at least one restriction enzyme, thereby providing restriction fragments;

 ligating adapter nucleic acids to the DNA restriction fragments;

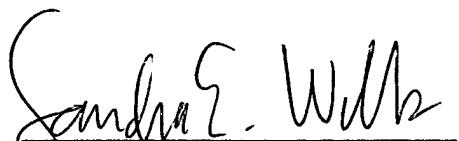
 providing primers that are complementary to the adapter nucleic acids; and,
 amplifying the DNA restriction fragments by the polymerase chain reaction by extending the primers, thereby providing the amplified nucleic acid mixture

Page 10, lines 5-16; Page 13, lines 20-24:
See passages above

If the Examiner has any further questions relating to this Amendment or to the application in general, he or she is respectfully requested to contact the agent of record by telephone.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Respectfully submitted,



Sandra E. Wells
Reg. No. 52,349

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Legal Department
Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051
Tel: 408/731-5000
Fax: 408/731-5392